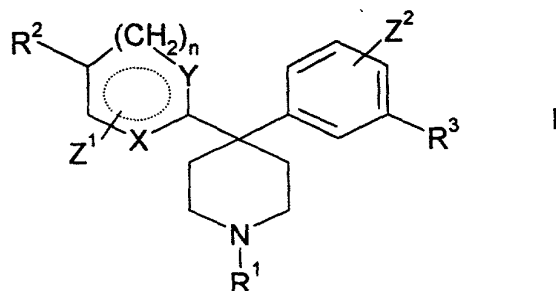


What is claimed is:

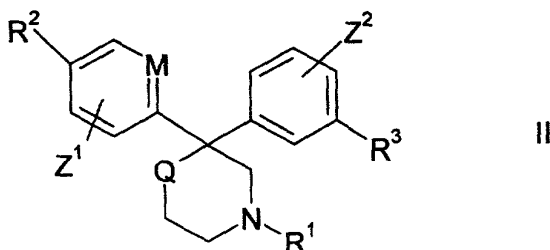
1. A method for treating a chemical dependency comprising administering an amount of a delta opioid receptor ligand and a serotonin reuptake inhibitor, said amounts being effective in said combination to treat said dependency, wherein said delta opioid receptor ligand is selected from the group consisting of:

a) a compound of the formula



10 and

b) a compound of the formula



- wherein  $X$  and  $Y$  are selected, independently, from oxygen, nitrogen, sulfur and  $CH$ , with the proviso that the ring in compound I containing  $X$  and  $Y$  must be aromatic and with the proviso that  $X$  and  $Y$  cannot both be either oxygen or sulfur;

$Q$  is oxygen or  $CH_2$ ;

$M$  is  $CH$  or  $N$ ;

$n$  is zero or one;

- $R^1$  is hydrogen,  $(C_0-C_8)$ alkoxy- $(C_0-C_8)$ alkyl-, wherein the total number of carbon atoms is eight or less, aryl, aryl- $(C_1-C_8)$ alkyl-, heteroaryl, heteroaryl- $(C_1-C_8)$ alkyl-, heterocyclic, heterocyclic- $(C_1-C_8)$ alkyl,  $(C_3-C_7)$ cycloalkyl-, or  $(C_3-C_7)$ cycloalkyl- $(C_1-C_8)$ alkyl, wherein said aryl and the aryl moiety of said aryl- $(C_1-C_8)$ alkyl- are selected, independently, from phenyl and naphthyl, and wherein said heteroaryl and the heteroaryl moiety of said heteroaryl- $(C_1-C_8)$ alkyl- are selected, independently, from pyrazinyl, benzofuranyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl,

1,2,5-thiadiazolyl, quinazolinyl, pyridazinyl, pyrazinyl, cinnolinyl, phthalazinyl, quinoxaliny, xanthinyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolyl, oxadiazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, pyrazolyl, pyrrolyl, tetrazolyl, triazolyl, thienyl, imidazolyl, pyridinyl, and pyrimidinyl; and wherein said heterocyclic and the heterocyclic moiety of said heterocyclic-(C<sub>1</sub>-C<sub>6</sub>)alkyl- are selected from saturated or unsaturated nonaromatic monocyclic or bicyclic ring systems, wherein said monocyclic ring systems contain from four to seven ring carbon atoms, from one to three of which may optionally be replaced with O, N or S, and wherein said bicyclic ring systems contain from seven to twelve ring carbon atoms, from one to four of which may optionally be replaced with O, N or S; and wherein any of the aryl, heteroaryl or heterocyclic moieties of R<sup>1</sup> may optionally be substituted with from one to three substituents independently selected from halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with from one to seven fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkylamino and [(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>amino, and wherein any of alkyl moieties in R<sup>1</sup> may optionally be substituted with from one to seven fluorine atoms;

R<sup>2</sup> is hydrogen, aryl, halo, heteroaryl, heterocyclic, SO<sub>2</sub>R<sup>4</sup>, COR<sup>4</sup>, CONR<sup>5</sup>R<sup>6</sup>, COOR<sup>4</sup>, or C(OH)R<sup>5</sup>R<sup>6</sup> wherein each of R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> is defined, independently, as R<sup>1</sup> is defined above, or R<sup>5</sup> and R<sup>6</sup>, together with the carbon or nitrogen to which they are both attached, form a three to seven membered saturated ring containing from zero to three heterocarbons selected, independently, from O, N and S, and wherein said aryl, heteroaryl, and heterocyclic are defined as such terms are defined above in the definition of R<sup>1</sup>, and wherein any of the aryl, heteroaryl and heterocyclic moieties of R<sup>2</sup> may optionally be substituted with from one to three substituents, independently selected from halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with from one to seven fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with from one to seven fluorine atoms, (C<sub>1</sub>-C<sub>6</sub>)alkylamino and [(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>amino;

R<sup>3</sup> is hydroxy, -(C<sub>1</sub>-C<sub>6</sub>)alkyl-OH, -OC(=O)R<sup>7</sup>, -(C<sub>1</sub>-C<sub>6</sub>)alkyl-(C<sub>1</sub>-C<sub>6</sub>)alkoxy, NHSO<sub>2</sub>R<sup>7</sup>, C(OH)R<sup>7</sup>R<sup>8</sup>, halo, or heteroaryl as defined for R<sup>1</sup> above or CONHR<sup>7</sup>, wherein R<sup>7</sup> and R<sup>8</sup> are the same or different and are selected from hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy and (C<sub>1</sub>-C<sub>4</sub>)alkoxy-(C<sub>1</sub>-C<sub>4</sub>)alkyl having a total of 4 or less carbon atoms, and wherein any of the alkyl moieties of R<sup>7</sup> and R<sup>8</sup> may optionally be substituted with from one to seven fluorine atoms; and

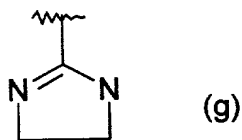
Z<sup>1</sup> and Z<sup>2</sup> are independently hydrogen, halo or (C<sub>1</sub>-C<sub>5</sub>)alkyl;

with the proviso that there are no two adjacent ring oxygen atoms and no ring oxygen atom adjacent to either a ring nitrogen atom or a ring sulfur atom in any of the heterocyclic or heteroaryl moieties of formula I or II;

and the pharmaceutically acceptable salts of such compounds.

2. A method according to claim 1 wherein said delta opioid receptor ligand is a compound of the formula I wherein n is zero or one; X and Y are both nitrogen; R<sup>1</sup> is benzyl, cyclopropylmethyl, 2-pyridyl, 4-fluoro-2-pyridyl, pyrimidyl, 2-methylpentyl, 3-phenylpropyl, 2-ethoxyethyl or 3,5,5-trimethylhexyl; R<sup>2</sup> is CON(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, CON(CH<sub>3</sub>)<sub>2</sub>, CON(CH<sub>2</sub>CH<sub>3</sub>)CH<sub>3</sub>, C(OH)(CH<sub>3</sub>)<sub>2</sub>, C(OH)(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, 3,3-dimethyloxazoline, 3,3-diethyloxazoline, benzoxazole, tetrazole or 3,5-dimethylpyrazole; and R<sup>3</sup> is OH, CONH<sub>2</sub>, fluoro, bromo, chloro, iodo, or NHSO<sub>2</sub>R<sup>7</sup>.

3. A method according to claim 1 wherein said delta opioid receptor ligand is a compound of the formula I wherein n is zero or one; X is nitrogen and Y is CH or oxygen; R<sup>1</sup> is benzyl, cyclopropylmethyl, 2-pyridyl, 4-fluoro-2-pyridyl, pyrimidyl, 2-methylpentyl, 3-phenylpropyl, 2-ethoxyethyl, 3,5,5-trimethylhexyl, allyl, cyclopropylmethyl, methyl, 2,2,2-trifluoroethyl, methallyl, isopropyl, 2-pyridinyl, 2-pyrimidinyl, or

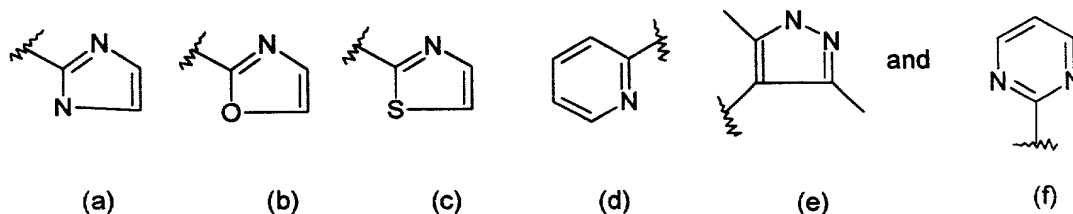


R<sup>2</sup> is CON(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, CON(CH<sub>3</sub>)<sub>2</sub>, CON(CH<sub>2</sub>CH<sub>3</sub>)CH<sub>3</sub>, C(OH)(CH<sub>3</sub>)<sub>2</sub>, C(OH)(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, 3,3-dimethyloxazoline, 3,3-diethyloxazoline, benzoxazole, tetrazole or 3,5-dimethylpyrazole; and R<sup>3</sup> is OH, CONH<sub>2</sub>, fluoro, bromo, chloro, iodo, or NHSO<sub>2</sub>R<sup>7</sup>.

4. A method according to claim 3 wherein n is zero, Y is CH, and R<sup>3</sup> is OH or CONH<sub>2</sub>.

5. A method according to claim 1 wherein said opioid receptor ligand is of the formula II wherein R<sup>1</sup> is cyclopropylmethyl, 3-cyclohexylpropyl, 2-phenylethyl, 2-methylpentyl, p-methylbenzyl, 2,2,2-trifluoroethyl, or 1-methylpentyl, R<sup>2</sup> is diethyl amide, methyl ethyl amide, a diethyl carbinol, tetrazole, or pyrazole, and R<sup>3</sup> is hydroxy, fluoro, CONH<sub>2</sub>, NHSO<sub>2</sub>CH<sub>3</sub>, or methoxy.

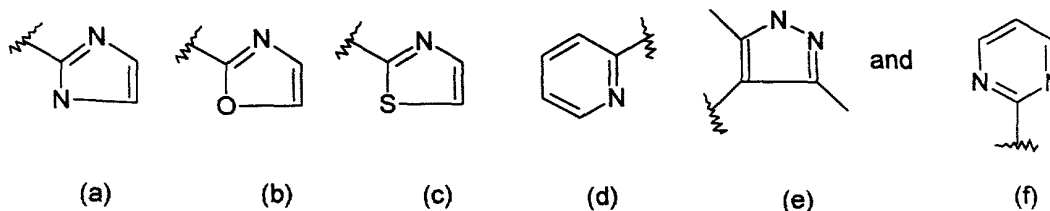
6. A method according to claim 1 wherein said opioid receptor ligand is of the formula II and Q is CH<sub>2</sub>, X is CH, R<sup>3</sup> is OH, CONH<sub>2</sub>, or fluoro, R<sup>2</sup> is selected from C(OH)(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, CON(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, CONCH<sub>3</sub>(C<sub>2</sub>H<sub>5</sub>) and the following cyclic groups:



and wherein Z<sup>1</sup> and Z<sup>2</sup> are selected, independently, from hydrogen and fluorine.

7. A method according to claim 1 wherein said opioid receptor ligand is selected from the group consisting of:

compounds of the formula II wherein Q is CH<sub>2</sub>, M is N, R<sup>3</sup> is OH, CONH<sub>2</sub>, or fluoro, and R<sup>2</sup> is selected from C(OH)(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, CON(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub> and one of cyclic groups (a) - (f):



5 compounds of the formula II wherein Q is oxygen, M is N, R<sup>3</sup> is OH, CONH<sub>2</sub>, or fluoro, and R<sup>2</sup> is selected from C(OH)(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>, CON(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub> and one of cyclic groups (a) - (f) depicted above;

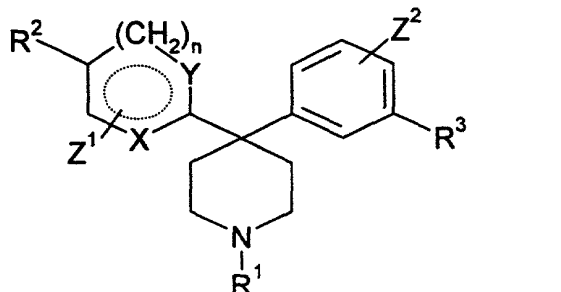
10 compounds of the formula II wherein Q is oxygen, M is CH, R<sup>3</sup> is OH, CONH<sub>2</sub> or fluoro, Z<sup>1</sup> and Z<sup>2</sup> or selected, independently, from hydrogen and fluoro, and R<sup>1</sup> is selected from allyl, cyclopropylmethyl, methyl, methallyl, isopropyl, 2-pyridinyl, 2-pyrimidinyl and cyclic group (g) depicted above; and

8. A method according to claim 1 wherein said opioid receptor ligand is a compound of the formula II wherein Q is oxygen, M is N, R<sup>3</sup> is OH, CONH<sub>2</sub> or fluoro, Z<sup>1</sup> and Z<sup>2</sup> or selected, independently, from hydrogen and fluoro, and R<sup>1</sup> is selected from allyl, cyclopropylmethyl, methyl, methallyl, isopropyl, 2-pyridinyl, 2-pyrimidinyl and cyclic group (g) depicted above.

9. A method of claim 1 wherein said serotonin reuptake ligand is selected from the group consisting of fluvoxamine, sertraline, citalopram, fluoxetine, paroxetine, imipramine, zimelidine, venlafaxine, and nefazodone.

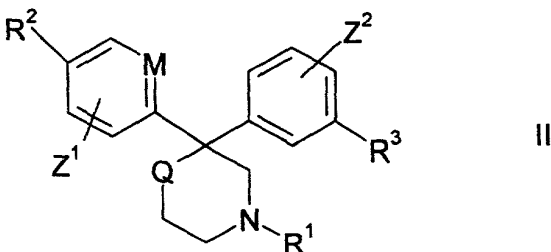
10. A pharmaceutical composition for the treatment of a chemical dependency wherein composition comprises amounts of a delta opioid receptor ligand and a serotonin reuptake inhibitor, said amounts being effective in said combination to treat said dependency, wherein said delta opioid receptor ligand is selected from the group consisting of

a) a compound of the formula



and

b) a compound of the formula



5            wherein X and Y are selected, independently, from oxygen, nitrogen, sulfur and CH,  
with the proviso that the ring in compound I containing X and Y must be aromatic and with the  
proviso that X and Y cannot both be either oxygen or sulfur;

Q is oxygen or CH<sub>2</sub>;

M is CH or N;

10            n is zero or one;

R<sup>1</sup> is hydrogen, (C<sub>0</sub>-C<sub>8</sub>)alkoxy-(C<sub>0</sub>-C<sub>8</sub>)alkyl-, wherein the total number of carbon atoms  
is eight or less, aryl, aryl-(C<sub>1</sub>-C<sub>8</sub>)alkyl-, heteroaryl, heteroaryl-(C<sub>1</sub>-C<sub>8</sub>)alkyl-, heterocyclic,  
heterocyclic-(C<sub>1</sub>-C<sub>8</sub>)alkyl, (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl-, or (C<sub>3</sub>-C<sub>7</sub>)cycloalkyl-(C<sub>1</sub>-C<sub>8</sub>)alkyl, wherein said  
aryl and the aryl moiety of said aryl-(C<sub>1</sub>-C<sub>8</sub>)alkyl- are selected, independently, from phenyl and  
15            naphthyl, and wherein said heteroaryl and the heteroaryl moiety of said heteroaryl-(C<sub>1</sub>-  
C<sub>8</sub>)alkyl- are selected, independently, from pyrazinyl, benzofuranyl, quinolyl, isoquinolyl,  
benzothienyl, isobenzofuryl, pyrazolyl, indolyl, isoindolyl, benzimidazolyl, purinyl, carbazolyl,  
1,2,5-thiadiazolyl, quinazolinyl, pyridazinyl, pyrazinyl, cinnolyl, phthalazinyl, quinoxalyl,  
xanthinyl, hypoxanthinyl, pteridyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl,  
20            imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, oxazolyl, oxadiazolyl, isoxazolyl,  
thiazolyl, isothiazolyl, furanyl, pyrazolyl, pyrrolyl, tetrazolyl, triazolyl, thienyl, imidazolyl,  
pyridinyl, and pyrimidinyl; and wherein said heterocyclic and the heterocyclic moiety of said  
heterocyclic-(C<sub>1</sub>-C<sub>8</sub>)alkyl- are selected from saturated or unsaturated nonaromatic monocyclic  
or bicyclic ring systems, wherein said monocyclic ring systems contain from four to seven ring  
25            carbon atoms, from one to three of which may optionally be replaced with O, N or S, and  
wherein said bicyclic ring systems contain from seven to twelve ring carbon atoms, from one  
to four of which may optionally be replaced with O, N or S; and wherein any of the aryl,  
heteroaryl or heterocyclic moieties of R<sup>1</sup> may optionally be substituted with from one to three  
substituents independently selected from halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with from one to  
30            seven fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-  
C<sub>6</sub>)alkylamino and [(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>amino, and wherein any of alkyl moieties in R<sup>1</sup> may optionally be  
substituted with from one to seven fluorine atoms;

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R<sup>2</sup> is hydrogen, aryl, halo, heteroaryl, heterocyclic, SO<sub>2</sub>R<sup>4</sup>, COR<sup>4</sup>, CONR<sup>5</sup>R<sup>6</sup>, COOR<sup>4</sup>, or C(OH)R<sup>5</sup>R<sup>6</sup> wherein each of R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> is defined, independently, as R<sup>1</sup> is defined above, or R<sup>5</sup> and R<sup>6</sup>, together with the carbon or nitrogen to which they are both attached, form a three to seven membered saturated ring containing from zero to three heterocarbons selected, independently, from O, N and S, and wherein said aryl, heteroaryl, and heterocyclic are defined as such terms are defined above in the definition of R<sup>1</sup>, and wherein any of the aryl, heteroaryl and heterocyclic moieties of R<sup>2</sup> may optionally be substituted with from one to three substituents, independently selected from halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted with from one to seven fluorine atoms, phenyl, benzyl, hydroxy, acetyl, amino, cyano, nitro, (C<sub>1</sub>-C<sub>6</sub>)alkoxy optionally substituted with from one to seven fluorine atoms, (C<sub>1</sub>-C<sub>6</sub>)alkylamino and [(C<sub>1</sub>-C<sub>6</sub>)alkyl]<sub>2</sub>amino;

R<sup>3</sup> is hydroxy, -(C<sub>1</sub>-C<sub>6</sub>)alkyl-OH, -OC(=O)R<sup>7</sup>, -(C<sub>1</sub>-C<sub>6</sub>)alkyl-(C<sub>1</sub>-C<sub>6</sub>)alkoxy, NHSO<sub>2</sub>R<sup>7</sup>, C(OH)R<sup>7</sup>R<sup>8</sup>, halo, or heteroaryl as defined for R<sup>1</sup> above or CONHR<sup>7</sup>, wherein R<sup>7</sup> and R<sup>8</sup> are the same or different and are selected from hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy and (C<sub>1</sub>-C<sub>4</sub>)alkoxy-(C<sub>1</sub>-C<sub>4</sub>)alkyl having a total of 4 or less carbon atoms, and wherein any of the alkyl moieties of R<sup>7</sup> and R<sup>8</sup> may optionally be substituted with from one to seven fluorine atoms; and

Z<sup>1</sup> and Z<sup>2</sup> are independently hydrogen, halo or (C<sub>1</sub>-C<sub>6</sub>)alkyl;

with the proviso that there are no two adjacent ring oxygen atoms and no ring oxygen atom adjacent to either a ring nitrogen atom or a ring sulfur atom in any of the heterocyclic or heteroaryl moieties of formula I;

and the pharmaceutically acceptable salts of such compounds.